



NDA 17-512/S-104 and S-106
NDA 20-163/S-012 and S-013
NDA 20-183/S-011 and S-012

Baxter Healthcare Corporation
Attention: Leslie Koehler
Director, Global Regulatory Affairs
1620 Waukegan Road
McGaw Park, IL 60085-6730

Dear Ms. Koehler:

Please refer to your supplemental new drug applications dated October 22, 2003 (NDA 17-512/S-104, NDA 20-163/S-012, and NDA 20-183/S-011), November 25, 2003 (NDA 20-163/S-013 and NDA 20-183/S-012) and March 23, 2005 (NDA 17-512/S-106) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Dianeal PD-2 Peritoneal Dialysis Solution Ambu-Flex III Plastic Containers (NDA 17-512/S-104)
- Dianeal Low Calcium Peritoneal Dialysis Solution Ambu-Flex III Plastic Containers (NDA 17-512/S-104)
- Dianeal PD-1 Peritoneal Dialysis Solution Ambu-Flex III Plastic Containers (NDA 17-512/S-106)
- Dianeal PD-2 Peritoneal Dialysis Solution UltraBag System (NDA 20-163/S-012 and S-013)
- Dianeal Low Calcium Peritoneal Dialysis Solution UltraBag System (NDA 20-183/S-011 and S-012)

We also acknowledge receipt of your July 15 and 30, 2004, and March 18, 2005 submissions.

Your submissions of March 18, 2005 constituted a complete response to our February 12, 2004 (NDA 17-512/S-104, NDA 20-163/S-012, and NDA 20-183/S-011) and March 26, 2004 (NDA 20-163/S-013 and NDA 20-183/S-012) approvable letters.

These supplemental new drug applications clarify the statements in the package insert concerning the proper method for heating the solution prior to administration and provide for use of an alternative connector with Baxter's UltraBag container-closure system, a comparability protocol for the use of the connector with additional fill sizes, and final printed labeling revised as follows:

NDA 17-512/S-104

Dianeal® Low Calcium Peritoneal Dialysis Solution Dianeal® PD-2 Peritoneal Dialysis Solution

1. All trademark symbols were removed throughout the package insert, and the following statement was placed at the end of the package insert:

Baxter, Dianeal, Ambu-Flex, and PL-146 are trademarks of Baxter International Inc.

2. Under the **Precautions** section, the following text was added:

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. Solutions should not be heated in water due to an increased risk of infection. Microwave ovens should not be used to heat solutions because there is a potential for damage to the solution container. Moreover, microwave oven heating may potentially cause overheating and/or non-uniform heating of the solution that may result in patient injury or discomfort.

3. Under the **Dosage and Administration** section, the following text was deleted:

Heating the dialysis solution to 37°C (98.6°F) may decrease discomfort and heat loss and result in increased clearances of urea when compared to solutions at room temperature (Gross and McDonald 1967).

and replaced with:

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. (See Directions for Use)

4. Under the **Directions for Use** section, the following text was deleted:

Warming the Dianeal® PD-2 solution, if desired, should be done in the overwrap using dry heat only. For patient comfort, the solution should be at body temperature (37°C/98.6°F). The solution container should be comfortably warm to the touch. Exceeding 45°C (113°F) solution temperature may be detrimental to the solution; do not overheat. If the warming method itself exceeds 45°C (113°F), frequently check the solution container and remove it from the heat source when the container becomes warm to the touch.

and replaced with:

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. Solutions should not be heated in water due to an increased risk of infection. Microwave ovens should not be used to heat solutions because there is a potential for damage to the solution container. Moreover, microwave oven heating may potentially cause overheating and/or non-uniform heating of the solution that may result in patient injury or discomfort.

Dianeal® Low Calcium Peritoneal Dialysis Solution

1. Under the **Warnings** section, paragraph ten, reference to 6 liters was inserted to read:

The use of 5 or 6 liters of dialysis solution is not indicated in a single exchange.

2. Under the **Warnings** section the following text was inserted:

Do not use 6 liter product with Pac-X or Pac-Xtra hardware.

3. Under the **How Supplied** section, paragraph one, the word “flexible” was added to the first sentence to read:

Dianeal Low Calcium peritoneal dialysis solutions in Ambu-Flex III containers are available in nominal size “flexible” containers with fill volumes as indicated in Table 1.

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4. Under the **How Supplied Columns, Table 1**, the 3000 ml and 6000 ml bags are added to include the fill volume, container size, code, and NDC for the respective bags.

5. The copyright text was deleted:

©Copyright 1981, 1982, 1983, 1984, 1987, Baxter Healthcare Corporation. All rights reserved.

7-19-4-217

Iss. July 1990

and replaced with:

©Copyright 1981, 1982, 1983, 1984, 1987, Baxter Healthcare Corporation. All rights reserved.

7-19-45-889

2005/02

Dianeal® PD-2 Peritoneal Dialysis Solution

1. The copyright text was deleted:

©Copyright 1981, 1982, 1983, 1984, 1989, Baxter Healthcare Corporation. All rights reserved.

7-19-3-647

Iss. 1997

and replaced with:

©Copyright 1981, 1982, 1983, 1984, 1987, Baxter Healthcare Corporation. All rights reserved.

7-19-45-887

2005/02

NDA 17-512/S-106

1. All trademark symbols were removed throughout the package insert, and the following statement was placed at the end of the package insert:

Baxter, Dianeal, Ambu-Flex, and PL-146 are trademarks of Baxter International Inc.

2. The text under the name of the label was deleted:

For intermittent Peritoneal Dialysis (IPD), Continuous Ambulatory Peritoneal Dialysis (CAPD), or Continuous Cyclic Peritoneal Dialysis (CCPD)

and replaced with:

AMBU-FLEX III Container For Peritoneal Dialysis

For intraperitoneal administration only

3. Under the **Description** section,

a. the second paragraph was deleted:

Composition, approximate osmolarity, approximate pH, and approximate ionic concentrations are shown in Table 1.

and replaced with:

Composition, calculated osmolarity, pH and ionic concentrations are shown in Table 1.

- b. the fifth paragraph, second sentence was deleted:

Water can permeate from inside the container into the overpouch in amounts insufficient to affect the solution significantly.

and replaced with:

The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly.

4. Under the **Clinical Pharmacology** section, second paragraph, the following text was deleted:

With the exception of lactate, which is present as a bicarbonate precursor, the ion concentration of electrolytes are similar to those in physiological extracellular fluid. Osmosis and diffusion occur across the peritoneal membrane between the plasma of the patient and the dialysis fluid. These processes result in plasma electrolyte concentrations which approach those found in the dialyzing fluid, and passage of toxic substances and metabolites, present in high concentrations in the blood, cross the peritoneal membrane into the dialyzing fluid.

and replaced with:

With the exception of lactate, present as a bicarbonate precursor, electrolyte concentrations in the fluid have been formulated to attempt to normalize plasma electrolyte concentrations resulting from osmosis and diffusion across the peritoneal membrane (between the plasma of the patient and the dialysis fluid). Toxic substances and metabolites, present in high concentrations in the blood, cross the peritoneal membrane into the dialyzing fluid.

5. Under the **Warnings** section,

- a. the following text was deleted:

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives, use aseptic technique. Mix thoroughly. Do not store.

- b. the following text was added:

The use of 5 liters of dialysis solution is not indicated in a single exchange.

6. Under the **Precautions** section,

- a. the following text was added:

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. Solutions should not be

heated in water due to an increased risk of infection. Microwave ovens should not be used to heat solutions because there is a potential for damage to the solution container. Moreover, microwave oven heating may potentially cause overheating and/or non-uniform heating of the solution that may result in patient injury or discomfort.

b. The Pregnancy: Teratogenic Effects Pregnancy Category C is now on the same line.

7. Under the **Dosage and Administration** section,

a. the following text was deleted:

Heating the dialysis solution to 37°C (98.6°F) may decrease discomfort and heat loss and result in increased clearances of urea when compared to solutions at room temperature (Gross and McDonald 1967).

and replaced with:

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. (See Directions for Use)

b. last paragraph, the following word “chronic” replaced the words “continuous ambulatory” to read:

It is recommended that adult patients being placed on chronic peritoneal dialysis or, in the case of pediatric patients, the selected caretaker, (as well as the patient, when suitable), should be appropriately trained in a program which is under the supervision of a physician.

8. Under the **How Supplied** section, the word flexible was added in the first sentence to read:

DIANEAL PD-1 peritoneal dialysis solutions in AMBU-FLEX III containers are available in nominal size flexible containers with fill volumes and dextrose concentrations as indicated in Table 1.

9. Under the **Directions for Use** section,

a. the following text was deleted:

Warming the Dianeal® PD-2 solution, if desired, should be done in the overwrap using dry heat only. For patient comfort, the solution should be at body temperature (37°C/98.6°F). The solution container should be comfortably warm to the touch. Exceeding 45°C (113°F) solution temperature may be detrimental to the solution; do not overheat. If the warming method itself exceeds 45°C (113°F), frequently check the solution container and remove it from the heat source when the container becomes warm to the touch.

and replaced with:

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. Solutions should not be heated in water due to an increased risk of infection. Microwave ovens should not be used to heat solutions because there is a potential for damage to the solution container. Moreover, microwave oven heating may potentially cause overheating and/or non-uniform heating of the solution that may result in patient injury or discomfort.

- b. under the **To Open** subheading, the following text was deleted:

Tear overpouch down side and slit and remove solution container.

and replaced with:

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety.

- c. under the **Preparation for Administration** subheading, the following step was revised and text added:

3. Attach appropriate solution transfer set. Refer to complete directions in hardware manual and/or directions accompanying transfer set.

Discard unused portion.

10. Under the **References**, the following reference was deleted:

Gross, M. and McDonald, Jr., H.P. 1967. Effect of dialysate temperature and flow rate on peritoneal clearance. JAMA 202:363-365.

11. Under **Table 1**,

- a. the row for Dianeal PD-1 Peritoneal Dialysis Solution with 3.5% Dextrose and the 500, 1000, 1500, 2500, and 3000 mL fill volume rows including the container size, Code, and NDC for each solution was deleted.

- b. the following column headings were changed respectively from:

APPROX. OSMOLARITY (mOsmol/L); APPROX. pH; APPROX. IONIC CONCENTRATION (MEq/L)

to:

Osmolarity (mOsmol/L)(calc); pH; Ionic concentration (MEq/L)

- c. the pH column of 5.5 was replaced by 5.2 (4.0 to 6.5).

- d. the 5000 mL fill volume was added to each of the solutions.

12. The sponsor information on the bottom left side of the label was updated to read:

Baxter Healthcare Corporation

Deerfield, IL 60015 USA

Printed in USA

13. The copyright text was deleted:

©Copyright 1981, 1982, 1983, 1984 Travenol Laboratories, Inc. All rights reserved.
8-19-4-691

Rev. March 1985

and replaced with:

©Copyright 1981, 1982, 1983, 1984, 1989, Baxter Healthcare Corporation. All rights reserved.
7-19-45-819
2005/02

NDA 20-163/S-012 and S-013
NDA 20-183/S-011 and S-012

1. All trademark symbols were removed throughout the package insert, and the following statement was placed at the end of the package insert:

Baxter, Dianeal, Ambu-Flex, and PL-146 are trademarks of Baxter International Inc.

2. The text under the name of the label was deleted:

UltraBag™ System For Continuous Ambulatory Peritoneal Dialysis (CAPD)
For intraperitoneal administration only

and replaced with:

UltraBag System with Luer Lock or **Lineo** Connector for Peritoneal Dialysis
For intraperitoneal administration only

3. Under the **Description** section,

- a. paragraph one, the following text was deleted:

They contain no bacteriostatic or antimicrobial agents.

and replaced with:

The peritoneal dialysis solutions contain no bacteriostatic or antimicrobial agents. The **Lineo** connector contains Povidine-iodine.

- b. the table listing the composition, osmolarity, ionic concentration, and how supplied lists container description for the Luer Lock and the Lineo Connector Products.
- c. a comma was deleted from the text in a column of the table under Composition to read Dextrose Hydrous, USP
- d. paragraph four, the word “tubing” replaced “Y” to read:

The plastic container tubing set is fabricated from polyvinyl chloride (**PL 146** Plastic).

- e. the following text was deleted:

Solutions in contact with the plastic container may leach out certain chemical

components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

and replaced with:

Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g. di 2-ethylhexyl phthalate (DEHP), at no more than 0.4 parts per million. This level is well below the daily, tolerable intake level established by the FDA for DEHP. Biological testing supports the safety of the plastic container materials.

4. Under the **Warning** section,

- a. third sentence, the word “patient” replaced the words “Luer lock” to read:

Contamination of the patient connector may result in peritonitis.

- b. the second to the last paragraph, the following text was deleted:

After the pull ring has been removed from the outlet, check for broken connector frangible seal as evidenced by continuous fluid flow from port. A few drops of solution within the connector or protector cap may be present. If a continuous stream or droplets of fluid are noted, discard solution because sterility may be impaired.

and replaced with:

After the pull ring has been removed from the outlet of the Luer lock system, check for broken connector frangible seal as evidenced by continuous fluid flow from port. A few drops of solution within the connector or protector cap may be present. If a continuous stream or droplets of fluid are noted with the Luer lock or **Lineo** Connector systems, discard solution because sterility may be impaired.

- c. the last paragraph, the following text was deleted:

During solution drainage, fibrin strands may be observed in the solution and may become attached to the connector frangible closure. In occasional instances, partial or complete obstruction of draining may occur. Manipulation of the connector frangible closure in the tubing may free the fibrin obstruction.

and replaced with:

During solution drainage, fibrin strands may be observed in the solution and may become attached to the blue connector frangible closure of the Luer lock system. In occasional instances, partial or complete obstruction of draining may occur. Manipulation of the connector frangible closure in the tubing may free the fibrin obstruction.

5. Under the **Precautions** section,

- a. General: Do not administer unless solution is clear.

and replaced with:

General: Do not administer unless solution is clear and protective closure is intact.

- b. the following text was added:

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. Solutions should not be heated in water due to an increased risk of infection. Microwave ovens should not be used to heat solutions because there is a potential for damage to the solution container. Moreover, microwave oven heating may potentially cause overheating and/or non-uniform heating of the solution that may result in patient injury or discomfort.

6. Under the **Dosage and Administration** section,

- a. the second sentence, the words “continuous ambulatory” before “peritoneal dialysis” was deleted to read:

It is recommended that adult patients being placed on peritoneal dialysis should be appropriately trained in a program which is under supervision of a physician.

- b. the following text was deleted:

Heating the dialysis solution to 37°C (98.6°F) may decrease discomfort.

and replaced with:

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. (See Directions for Use)

7. Under the **Directions for Use/Preparation for Administration** section, the steps were renumbered and the following step was added:

- a. 2. Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) to enhance patient comfort. However, only dry heat (for example, heating pad) should be used. Solutions should not be heated in water due to an increased risk of infection. Microwave ovens should not be used to heat solutions because there is a potential for damage to the solution container. Moreover, microwave oven heating may potentially cause overheating and/or non-uniform heating of the solution that may result in patient injury or discomfort.

- b. the following step was deleted:

5. Inspect the patient connector to ensure the pull ring is attached. Do not use if pull ring is not attached to the connector.

and replaced with:

6. Inspect the patient connector to ensure the protective closure is attached. Do not use if the protective closure is not attached to the connector.

8. Under the **Directions for Use/Administration** section,

- a. subheadings, **Connect and Begin Therapy**, **Disconnect from Luer Lock**

System, and **Disconnect from LINEO System** were added.

- b. the following step in the **Connect and Begin Therapy** subsection was deleted:

3. Break connector frangible (blue) by grasping the tubing above the top of the frangible and pulling forward and backward until the frangible separates from base. See Figures 1 and 2.

and replaced with:

3. For Luer Lock System only, break connector frangible (blue) by grasping the tubing above the top of the frangible and pulling forward and backward until the frangible separates from base. (Note: The blue frangible is not incorporated in the **Lineo** System)

- c. the following step was deleted:

4. Remove pull ring from the patient connector.

and replaced with:

4. Remove protective closure from the patient connector.

- d. the second sentence of step 5 was deleted:

Immediately attach patient transfer set connector to the patient connector by twisting the connector until firmly secured.

and replaced with:

Immediately attach patient transfer set to the patient connector by twisting the patient connector until firmly secured.

- e. “See Figures 3 and 4.” was deleted from step 7.

- f. the following step was deleted:

10. Open transfer set clamp to drain solution from peritoneum. **Warning:** During solution drainage, fibrin strands may become attached to the connector frangible closure. Manipulation of the connector frangible closure in the tubing may free any fibrin obstruction that occurs.

and replaced with:

10. Open transfer set clamp to drain solution from peritoneum. **Warning:** During solution drainage with the Luer Lock System, fibrin strands may become attached to the connector frangible closure. Manipulation of the connector frangible closure in the tubing may free any fibrin obstruction that occurs.

9. Under the **Directions for Use** section, the following steps were deleted:

15. Close transfer set clamp when infusion is complete.

16. Prepare a new disconnect cap following the directions accompanying the cap.

17. Disconnect the patient transfer set connection from the UltraBag™ and attach a new disconnect cap to the transfer set.

and replaced with two separate disconnecting steps for both the Luer Lock and **Lineo** Systems:

Disconnect from Luer Lock System:

1. Close transfer set clamp when infusion is complete.
2. Prepare a new disconnect cap following the directions accompanying the cap.
3. Disconnect the patient transfer set connection from the **UltraBag** and attach a new disconnect cap to the transfer set.

Disconnect from the Lineo System:

1. Close transfer set clamp when infusion is complete.
2. Disconnect the patient transfer set from the **UltraBag**. Note: Upon disconnect, **Lineo** cap will remain on patient transfer set.
3. Ensure **Lineo** cap is secure.

10. Figures and diagrams were deleted.

NDA 20-163/S-012 and S-013

1. Under the **Indications and Usage** section, the following text was deleted:

Dianeal® PD-2 peritoneal dialysis solutions in UltraBag™ containers are indicated for use in chronic renal failure patients being maintained on continuous ambulatory peritoneal dialysis when nondialytic medical therapy is judged to be inadequate.

and replaced with:

Dianeal PD-2 peritoneal dialysis solutions in **UltraBag** containers are indicated for use in chronic renal failure patients being maintained on peritoneal dialysis when nondialytic medical therapy is judged to be inadequate.

2. Under the **Precautions** section,

a. The text following General is now on the same line.

b. carcinogenesis paragraph, the following text was deleted:

Long term animal studies with Dianeal® PD-2 peritoneal dialysis solution have not been performed to evaluate the carcinogenic potential, mutagenic potential or effect on fertility.

and replaced with:

Studies to evaluate the carcinogenic or mutagenic potential of this product, or its potential to affect fertility adversely, have not been performed.

3. The copyright text was deleted:

©Copyright 1992, 1994, Baxter Healthcare Corporation. All rights reserved.

7-19-3-253

Iss. 1995

and replaced with:

©Copyright 1992, 1994, 2004, Baxter Healthcare Corporation. All rights reserved.

7-19-44-674

2005/03

NDA 20-183/S-011 and S-012

1. Under the **Description** section, the table row entitled “Dianeal Low Calcium Peritoneal Dialysis Solution with 3.5% Dextrose” was deleted.

2. Under the **Indications and Usage** section, the following text was deleted:

Dianeal® Low Calcium peritoneal dialysis solutions in UltraBag™ containers are indicated for use in chronic renal failure patients being maintained on continuous ambulatory peritoneal dialysis when nondialytic medical therapy is judged to be inadequate.

and replaced with:

Dianeal Low Calcium peritoneal dialysis solutions in **UltraBag** containers are indicated for use in chronic renal failure patients being maintained on peritoneal dialysis when nondialytic medical therapy is judged to be inadequate.

3. Under the **Warnings** section, paragraph six, reference to 3.5% dextrose was deleted to read:

Excessive use of Dianeal® Low Calcium peritoneal dialysis solution with 4.25% dextrose during a peritoneal dialysis treatment can result in significant removal of water from the patient.

4. Under the **Precautions** section, carcinogenesis paragraph, the following text was deleted:

Long term animal studies with Dianeal® Low Calcium peritoneal dialysis solution have not been performed to evaluate the carcinogenic potential, mutagenic potential or effect on fertility.

and replaced with:

Studies to evaluate the carcinogenic or mutagenic potential of this product, or its potential to affect fertility adversely, have not been performed.

5. Under the **Dosage and Administration** section, last paragraph, the following text was deleted:

The majority of exchanges will utilize 1.5% or 2.5% dextrose containing peritoneal dialysis solutions with 3.5% or 4.25% dextrose containing solutions being used when extra fluid removal is required.

and replaced with:

The majority of exchanges will utilize 1.5% or 2.5% dextrose containing peritoneal dialysis solutions with 4.25% dextrose containing solutions being used when extra fluid removal is required.

6. The copyright text was deleted:

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7-19-3-254
Iss. 1995

and replaced with:

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7-19-44-671
2005/3

We completed our review of these supplemental new drug applications. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on March 18, 2005 (NDA 17-512/S-104, NDA 20-163/S-012 and S-013, and NDA 20-183/S-011 and S-012) and March 23, 2005 (NDA 17-512/S-106).

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call
Ms. Dianne Paraoan
Regulatory Project Manager
(301) 594-5308

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office for Drug Evaluations I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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